The majority of patients (31 of 53 patients; 58%) received 4 of 4 PS-341 doses in both Cycles 1 and 2. The mean number of total doses administered, the mean duration of treatment and the mean number of cycles completed were similar across the 6 lowest dose levels (0.13 to 1.80 mg/m2). Patients at the 2.00 mg/m2 dose level had on average the shortest duration of treatment and lowest number of completed cycles as compared to the other 6 dose levels evaluated.

All (100%) 53 patients experienced at least 1 treatment-emergent adverse event during the study. The most commonly reported adverse events were diarrhea NOS (28 patients; 53%), fatigue (27 patients; 51%), constipation (25 patients; 47%), nausea (22 patients; 42%); vomiting NOS (18 patients; 34%), catheter-related complication (15 patients, 28%), back pain (15 patients; 28%), weakness (14 patients; 26%), abdominal pain NOS, bone pain, and pyrexia (13 patients each; 25%).

Diarrhea was the most commonly reported adverse event overall, occurring in 28 (53%) of 53 patients and also was one of the most commonly reported drug-related events (24 of 53 patients, 45%) and event of Grade 3 or 4 severity (7 patients, 13%). The incidence of diarrhea or loose stools was highest among patients at the highest dose levels, with ≥67% of patients at each of the 0.13-0.60, 0.75-0.90, 1.00-1.32 and 1.45 mg/m2 dose levels experiencing diarrhea or loose stools compared to >90% of patients at the 1.60, 1.80, and 2.00 mg/m2 dose levels. The intensity of the diarrhea was also greater at the highest dose levels. None of the patients at the 0.13-0.60, 0.75-0.90, 1.00-1.32 and 1.45 mg/m2 dose levels experienced Grade 3 diarrhea compared to 31%, 50%, and 40% of patients at the 1.60, 1.80 and 2.00 mg/m2 dose levels. Five patients, including 1 (17%) of 6 at the 1.45 mg/m2 dose level, 3 (23%) of 13 at the 1.60 mg/m2 dose level and 1 (20%) of 5 at the 2.00 mg/m2 dose level, experienced diarrhea that was reported as serious in nature. The first onset of diarrhea occurred most commonly during Cycles 1 or 2. In most patients the diarrhea was self-limiting or controlled with loperamide or diphenoxylate with atropine. Three (6%) patients discontinued study treatment due to diarrhea.

Those 29 patients with diarrhea and/or loose stools reported as an adverse event also were likely to experience other gastrointestinal side effects, including constipation, nausea, and vomiting. Overall, constipation was reported in 25 (47%) patients; in 20 (38%) patients, the event was assessed as drug-related by the investigator. All 5 patients at the 2mg/m^2 dose level did experience this gastrointestinal symptom. Nausea was reported in 22 (42%) patients and was assessed as drug-related in 16 (30%) patients. The reported incidence of nausea was similar across the 7 dose levels. All reports of constipation and nausea were Grade 1 or 2 in severity. Vomiting occurred in 18 (34%) of 53 patients; in 14 (26%) patients, the vomiting was assessed as drug-related. One patient experienced Grade 3 vomiting that was assessed as unrelated to study treatment; all other reports were Grade 1 or 2 in severity.

Twenty-seven (51%) of 53 patients experienced fatigue during the study. The incidence of fatigue was lowest in the 3 lowest PS-341 dose groups occurring in 30%, 11%, and 25% of patients in the 0.13-0.60, 0.75-0.90 and 1.00-1.32 mg/m^2 dose levels, respectively, compared to dose) were reported. Both of

these patients were discontinued due to the hypotension. In the latter patient, grade 3 diarrhea had been reported prior to onset of the orthostatic the 4 highest dose levels with incidence rates of 83%. 85%, 50% and 80% of patients at the 1.45, 1.6, 1.8 and 2.00 mg/m^2 dose levels, respectively. The majority of reported cases of fatigue were Grade 1 or 2 in intensity; 3 patients experienced Grade 3 fatigue.

Overall, the incidence of hematologic toxicity in this study was modest. There was no apparent relationship between dose of VELCADE and the incidence of blood and lymphatic system disorders.Drug-related events in this SOC were reported in 6 (11%) patients and included 2 reports of thrombocytopenia and one report each of anemia, lymphocytopenia, granulocytopenia, and leukopenia.

Hypotension was reported as an adverse event in 10 (19%) of the 53 patients. There was no apparent increase in the incidence of hypotension across dose levels with 30%, 11%, 0%, 17%, 31%, 50% and 0% of patients in the 0.13-0.60, 0.75-0.90, 1.00-1.32, 1.45, 1.6, 1.8 and 2 mg/m^2 dose levels experiencing this event. Two patients, 1 in the 0.13-0.60 mg/m^2 dose level and 1 in the 1.45 mg/m^2 dose level experienced postural hypotension and 1 patient in the 2 mg/m^2 dose level experienced orthostatic hypotension. Most reports of hypotension occurred during Cycle 1; only 2 patients had hypotension reported after this cycle. The majority of reports of hypotension were Grade 1 or 2 in intensity. One episode of Grade 3 hypotension (Patient 31, 1.60 mg/m^2 dose) and 1 of Grade 3 orthostatic hypotension (Patient 53, 2 mg/m2 dose) were reported. Both of these patients were discontinued due to the hypotension. In the latter patient, grade 3 diarrhea had been reported prior to onset of the orthostatic hypotension; this event was also associated with a possible syncopal episode.

Two cases of peripheral sensory-type neuropathy were reported. Grade 3 dysesthesia (burning feet) that led to study discontinuation was reported in one patient at the 2 mg/m^2 dose level and Grade 3 peripheral sensory neuropathy was reported in one patient at the 1.45 mg/m^2 dose level.

One patient death was reported within 30 days of the last study drug dose. Patient No. 31 (1.60 mg/m^2) died 23 days after the last dose of PS-341. The cause of death was reported as cancer/severe respiratory distress; the death was assessed as unrelated to study treatment by the investigator.

There was no apparent increase in the overall incidence of serious adverse events (SAEs) with increasing dose level. Overall, 21 (40%) of 53 patients experienced at least 1 serious adverse event during the study. Treatment was discontinued by 11%, 13%, 33%, 31% and 40% of patients in the 0.75-0.90 mg/m^2, 1.00-1.32 mg/m^2, 1.45 mg/m^2, 1.60 mg/m^2, and 2.00 mg/m^2 dose levels, respectively, due to adverse events. The most commonly reported adverse events leading to discontinuation were diarrhea NOS (3 patients, 6%) and postural/orthostatic hypotension (2 patients, 4%). In general, mean values of vital signs (systolic and diastolic blood pressure, temperature, pulse rate, respiration rate) were within the normal range at baseline and

at all post-dose time points assessed at all PS-341 dose levels. Furthermore, no apparent trend was seen within or among dose levels with regard to change from baseline to the end of Cycle 1 (after 4 PS-341 doses) or Cycle 2 (8 PS-341 doses) for any vital signs parameters.

VELCADE's effect on proteasome inhibition was measured in peripheral blood lymphocytes as a pharmacodynamic indicator of interest. The percent inhibition versus toxicity suggests a trend, as shown in the sponsor's table. Proteasome inhibition levels above 70% were associated with more toxicity, but the confidence intervals (CI) are wide and overlapping.

Table 34: Frequency of Toxicity by Degree of Proteasome Inhibition (ChT:T)

		PS-341 Percent Proteasome Inhibition in blood lymphocytes		
Parameter	Statistic	< 70% N=37	70% to < 80% N=7	>= 80% N=0
Occurrence of DLT	N (%)	2 (5)	2 (29)	0
	90% CI	1.0, 16.1	5.3, 65.9	
Occurrence of Any Grade ¾ Adverse Event	N (%)	24 (65)	6 (86)	0
	90% CI	50.0, 77.8	47.9, 99.3	
Occurrence of Any Serious Adverse Event	N (%)	14 (38)	4 (57)	0
	90% CI	24.5, 52.7	22.5, 87.1	
Discontinuation due to Adverse Event	N (%)	6 (16)	3 (43)	0
	90% CI	7.3, 29.5	12.9, 77.5	

sponsor's table 14.3.1.8 protocol DM98-194 module 5.3.4.2.1

Study 98-104A:

Study 98-104A was a phase 1, dose escalation study designed to determine the DLT and MTD of PS-341 administered as an IV bolus in 3-week treatment cycles consisting of PS-341 administration twice weekly for 2 consecutive weeks (on Days 1, 4, 8, and 11) followed by a 10-

day rest period. DLT was defined as any Grade 4 hematologic toxicity or any Grade 3 non-hematologic toxicity, with the exception of hyperbilirubinemia and alopecia, that occurred during Cycle 1 and was considered by the investigator to be at least possibly related to study drug. The MTD was defined as the highest dose studied at which none of 3 or 1 of 6 patients experienced a DLT.

The mean total dose of PS-341 administered in this study of 43 patients was 12.2 mg, with a range of 1 to 41 mg. The mean number of PS-341 doses administered was 8 (range 1 to 24) and the mean duration of treatment (i.e., from first dose to last dose of PS-341) was 5 weeks (range 1 day to ~4 months).

A total of 43 patients with advanced malignancies was enrolled in this study at a single study site in the United States. Approximately half of patients were female (56%). The majority of patients were white (79%), and the mean age of patients was 54 years. Diagnoses at study entry included lung carcinoma (19%); colon carcinoma (14%); head and neck, prostate, and renal carcinoma and melanoma (each 9%); endometrial and pancreatic carcinoma (each 5%); and bladder, cervical, esophageal, and gastric carcinoma (each 2%). Five percent (5%) of patients had primary cancer of unknown origin. The mean duration of time since disease diagnosis was 4 years, and patients were, in general, heavily pre-treated, with a mean and median number of previous treatment regimens of 3.7 and 3, respectively.

The following sponsor's table shows the drug exposure (duration of treatment, number of cycles, number of doses, and total doses study patients received.)

Table 35: Dosing Information: Study 98-104A

		PS-341 Dose Groups (mg/m²)									
	Statistic	0.13 N = 3	0.25 N = 4	0.4 N = 5	0.6 N = 4	0.75 N = 3	0.9 N = 6	1.08 N = 3	1.30 N = 3	1.56 N = 12	Total N = 43
Duration of Treatment* (days)	N	3	4	5	4	3	6	3	3	12	43
	Mean	32.0	39.0	24.4	31.3	55.7	59.3	31.0	40.3	22.2	34.9
	Std Dev	0.00	26.19	18.09	29.74	24.11	44.26	1.73	31.72	17.75	26.78
	Median	32.0	35.5	32.0	20.0	53.0	33.0	32.0	36.0	18.5	32.0
	Minimum	32.0	11.0	1.0	11.0	33.0	32.0	29.0	11.0	4.0	1.0
	Maximum	32.0	74.0	46.0	74.0	81.0	137.0	32.0	74.0	67.0	137.0
Number of Cycles**	N	3	4	5	4	3	6	3	3	12	43
	Mean	2.0	2.3	1.6	2.0	3.0	2.8	2.0	2.3	1.6	2.1
	Std Dev	0.00	1.26	0.55	1.41	1.00	1.60	0.00	1.53	0.67	1.06
	Median	2.0	2.0	2.0	1.5	3.0	2.0	2.0	2.0	1.5	2.0
	Minimum	2.0	1.0	1.0	1.0	2.0	2.0	2.0	1.0	1.0	1.0
	Maximum	2.0	4.0	2.0	4.0	4.0	6.0	2.0	4.0	3.0	6.0
Number of Doses	N	3	4	5	4	3	6	3	3	12	43
	Mean	8.0	9.0	5.8	7.8	12.0	11.0	7.7	9.0	5.7	7.9
	Std Dev	0.00	5.03	3.19	5.68	4.00	6.42	0.58	6.24	2.90	4.42
	Median	8.0	8.0	8.0	5.5	12.0	8.0	8.0	7.0	5.0	8.0
	Minimum	8.0	4.0	1.0	4.0	8.0	8.0	7.0	4.0	2.0	1.0
	Maximum	8.0	16.0	8.0	16.0	16.0	24.0	8.0	16.0	12.0	24.0
	Statistic	0.13 N = 3	0.25 N = 4	0.4 N = 5	0.6 N = 4	0.75 N = 3	0.9 N = 6	1.08 N = 3	1.30 N = 3	1.56 N = 12	Total N = 43
Total Dose (mg)	N	3	4	5	4	3	6	3	3	12	43
	Mean	1.6	3.5	3.7	7.2	17.9	18.1	14.8	19.5	16.2	12.2
	Std Dev	0.09	1.82	1.83	4.70	8.12	11.37	1.39	13.14	8.75	9.56
	Median	1.5	3.1	4.6	5.5	14.6	12.8	15.2	17.3	14.8	12.0
	Minimum	1.5	1.8	0.7	4.0	12.0	12.0	13.3	7.6	5.5	0.7
	Maximum	1.7	6.1	5.2	14.1	27.2	40.8	16.0	33.6	36.5	40.8
Total Dose in Cycle 1 (mg/m²)	N	3	4	5	4	3	6	3	3	12	43
	Mean	0.8	1.6	2.2	3.9	5.9	6.5	7.7	8.6	10.5	6.2
	Std Dev	0.05	0.11	0.89	0.38	0.96	0.47	0.23	1.16	2.32	3.75
	Median	0.8	1.6	2.4	3.8	6.0	6.4	7.6	8.4	10.7	6.4
	Minimum	0.8	1.5	0.7	3.5	4.9	6.0	7.6	7.6	5.5	0.7
	Maximum	0.8	1.8	3.1	4.4	6.8	7.2	8.0	9.9	13.2	13.2

Sponsor's table 14.1.6

•Duration is days from first dose day to last dose day inclusive.
** One complete cycle in this schedule is 4 doses.

Note: The planned cumulative VELCADE dose per cycle was 0.52 mg/m^2 at the 0.13 dose level; 1.0 mg/m^2 at the 0.25 dose level; 1.6 mg/m^2 at the 0.40 dose level; 2.4 mg/m^2 at the 0.60 dose level; 3.0 mg/m^2 at the 0.75 dose level; 3.6 mg/m^2 at the 0.90 dose level; 4.3 mg/m^2 at the 1.08 dose level; 5.2 mg/m^2 at the 1.30 dose level; and 6.2 mg/m^2 at the 1.56 dose level.

All 43 patients experienced at least 1 treatment-emergent adverse event during the study. The most commonly reported adverse events were hemoglobin decreased (34 patients; 79%), fatigue (28 patients; 65%), constipation (19 patients; 44%), nausea (19 patients; 44%), and platelet count decreased (15 patients; 35%). Seventeen (40%) of 43 patients experienced at least 1 adverse event of ≥grade 3 intensity. Commonly reported ≥grade 3 adverse events included diarrhea and peripheral sensory neuropathy (4 patients each; 9%) and dyspnea and hemoglobin decreased (3 patients each; 7%). All other grade 3 adverse events were reported by 2 patients or fewer. Three (7%) of 43 patients experienced an adverse event of grade 4 intensity during the study; grade 4 adverse events reported included single episodes of large intestinal obstruction, constipation, and dyspnea. All grade 4 adverse events were considered by the investigator to be unrelated to study drug. Hemoglobin decreased (i.e., anemia), the most commonly reported adverse event overall, also was the most commonly reported adverse event considered by the investigator to be at least possibly related to study drug. Of the 34 patients who experienced anemia, 32 experienced at least 1 episode that was considered by the investigator to be study drug-related. The majority of these 34 patients (22 patients; 65%) had anemia at baseline. Most episodes of anemia that occurred during the study were Grade 1 or 2 in intensity. Overall, 3 (7%) of 43 patients experienced at least 1 episode of Grade 3 anemia, 1 patient each at the 0.25, 1.30, and 1.56 mg/m^2 levels (Patient Nos. 4, 29, and 37, respectively). All 3 patients required RBC transfusions for the management of grade 3 anemia. No patient experienced grade 4 anemia during the study. Three additional patients received RBC transfusions for the management of anemia, 1 patient each at the 0.60 mg/m^2 dose level, 1.08 mg/m^2 dose level, and 1.56 mg/m^2 dose level.

During the study, 28 (65%) of 43 patients experienced at least 1 episode of fatigue. Nineteen (44%) of 43 patients experienced treatment-emergent constipation during the study. Of these 19 patients, 15 received concomitant treatment with opiates or derivatives during the study. Four (9%) of 43 patients, all of whom were at the 1.56 mg/m^2 level, experienced at least 1 episode of constipation that was considered by the investigator to be at least possibly related to study drug. Most constipation was mild or moderate (Grade 1 or 2) in intensity, manageable with stool softeners or laxatives, and considered by the investigator to be unrelated to study drug. One (2%) of 43 patients experienced Grade 3 constipation during the study. Patient No. 16 (0.60 mg/m^2) who had a primary diagnosis of colon cancer, experienced Grade 4 constipation in Cycle 4, which was considered by the investigator to be unrelated to study drug. No other patient experienced grade 3 constipation during the study. No apparent trend was seen with regard to the time to onset of constipation.

No patient died during the study or within 30 days after the last study drug dose. Overall, approximately one-fourth of patients (11 of 43; 26%) experienced at least 1 serious adverse event during the study or within 30 days after the last study drug dose: 2 (50%) of 4 patients at the 0.25 mg/m^2 level; 2 (40%) of 5 patients at the 0.40 mg/m^2 level; 2 (67%) of 3 patients at the 1.08 mg/m^2 level; 1 (33%) of 3 patients at the 1.30 mg/m^2 level; and 4 (33%) of 12 patients at the 1.56 mg/m^2 level. There was no apparent dose relationship for the incidence of serious adverse events. Furthermore, no apparent trend was seen with regard to the incidence of particular serious adverse events.

Overall, 7 (16%) of 43 patients discontinued study drug because of adverse events/excessive toxicity, 1 (25%) of 4 patients at the 0.60 mg/m^2 level, 1 (33%) of 3 patients at the 1.30 mg/m^2 level, and 5 (42%) of 12 patients at the 1.56 mg/m^2 level. At least 1 adverse event leading to study drug discontinuation was Grade 3 in intensity for 4 patients; for all 4 patients, at least 1 of the Grade 3 adverse events leading to study drug discontinuation also was reported as serious. Two patients, 1 each at the 1.30 and 1.56 mg/m^2 levels, had serious adverse events leading to study drug discontinuation that were considered by the investigator to be definitely related to study drug; both of these patients discontinued from the study because of peripheral neuropathy (MedDRA preferred terms: peripheral sensory neuropathy and peripheral neuropathy NOS).

Reviewer's comments: The next 2 sponsor's tables below show the treatment-emergent adverse events by dose level reported by at least 10% of patients and the drug-related treatment-emergent adverse events of grade 3 or 4 severity. The most frequently reported adverse events were hemoglobin decreased, fatigue, platelet count decreased, and GI complaints (constipation, nausea, vomiting).

Table 36: Treatment-Emergent Adverse Events Reported by ≥10% of Patients,

Overall and By Relationship to Study Drug and Intensity

	N = 43	**PS-341-Treated Patients (N=43)**	
MedDRA Preferred Term	**Total n (%)**	**Study Drug-Related[a] n (%)**	**>Grade 3[b] n (%)**
Patients with at least 1 adverse event	43 (100)	39 (91)	17 (40)
Hemoglobin decreased	34 (79)	32 (74)	3 (7)
Fatigue	28 (65)	16 (37)	2 (5)
Constipation	19 (44)	4 (9)	1 (2)
Nausea	19 (44)	11 (26)	0
Platelet count decreased	15 (35)	15 (35)	2 (5)
Vomiting NOS	15 (35)	8 (19)	0
Diarrhea NOS	13 (30)	10 (23)	4 (9)
Anorexia	11 (26)	5 (12)	0
Dyspnea NOS	11 (26)	0	3 (7)
Pyrexia	11 (26)	9 (21)	0
Abdominal pain NOS	9 (21)	3 (7)	2 (5)
Headache NOS	9 (21)	6 (14)	0

Peripheral sensory neuropathy	8 (19)	5 (12)	4 (9)
White blood cell count decreased	7 (16)	7 (16)	1 (2)
Anxiety NEC	5 (12)	0	0
Dizziness (excl. vertigo)	5 (12)	1 (2)	0
Myalgia	5 (12)	3 (7)	1 (2)
Edema	5 (12)	0	0
Weight decreased	5 (12)	0	0

Sponsor's table 12.3 protocol 98-104A
Source: Section 14.3, Table 14.3.1.2, Table 14.3.1.3, and Table 14.3.1.4.
NOS = Not otherwise specified. NEC = Not elsewhere classified.
a Adverse events considered by the investigator to be at least possibly related to study drug
b All adverse events considered by the investigator to be Grade 3 or 4 according to the NCI CTC regardless of relationship to study drug.

Table 37: Treatment-Emergent Adverse Events Reported by ≥10% of Patients Overall by Dose Group

N = 43	study 98-104A PS-341 Dose Group (mg/m^2)					
MedDRA Preferred Term	**≤0.25 (n=7) n (%)**	**0.40 - 0.60 (n=9) n (%)**	**>0.60 – 1.00 (n=9) n (%)**	**>1.00 - <1.50 (n=6) n (%)**	**≥1.50 (n=12) n (%)**	**Total (n=43) n (%)**
Patients with at least adverse event	7 (100)	9 (100)	9 (100)	6 (100)	12 (100)	43 (100)
Hemoglobin decreased	5 (71)	7 (78)	5 (56)	6 (100)	11 (92)	34 (79)
Fatigue	5 (71)	6 (67)	5 (56)	2 (33)	10 (83)	28 (65)
Constipation	3 (43)	4 (44)	3 (33)	3 (50)	6 (50)	19 (44)
Nausea	0	2 (22)	3 (33)	3 (50)	11 (92)	19 (44)
Platelet count decreased	0	2 (22)	3 (33)	3 (50)	7 (58)	15 (35)
Vomiting NOS	0	3 (33)	2 (22)	3 (50)	7 (58)	15 (35)
Diarrhea NOS	0	1 (11)	2 (22)	3 (50)	7 (58)	13 (30)
Anorexia	0	1 (11)	1 (11)	3 (50)	6 (50)	11 (26)
Pyrexia	0	3 (33)	2 (22)	2 (33)	4 (33)	11 (26)
Dyspnea NOS	1 (14)	1 (11)	2 (22)	3 (50)	4 (33)	11 (26)
Abdominal pain NOS	1 (14)	1 (11)	2 (22)	1 (17)	4 (33)	9 (21)
Headache NOS	2 (29)	0	1 (11)	0	6 (50)	9 (21)
Peripheral sensory neuropathy	0	1 (11)	1 (11)	2 (33)	4 (33)	8 (19)
WBC decreased	1 (14)	2 (22)	1 (11)	1 (17)	2 (17)	7 (16)
Anxiety NEC	0	1 (11)	1 (11)	1 (17)	2 (17)	5 (12)
Dizziness (excl. vertigo)	0	1 (11)	1 (11)	1 (17)	2 (17)	5 (12)
Myalgia	1 (14)	0	2 (22)	1 (17)	1 (8)	5 (12)

Edema NOS	0	1 (11)	1 (11)	2 (33)	1 (8)	5 (12)
Weight decreased	0	1 (11)	1 (11)	2 (33)	1 (8)	5 (12)

sponsor's table 12.5 protocol 98-104A

Seven patients required treatment for nausea; all 7 patients were in the 1.50 mg/m^2 group. Treatments administered for nausea included prochlorperazine, granisetron, omeprazole, magnesium oxide, and lorazepam. Treatment for nausea was administered orally for 6 of 7 patients; 1 patient received granisetron intravenously. Nausea was accompanied by vomiting for 12 patients, 2 patients in the >0.60 to 1.00 mg/m^2 group, 3, patients in the >1.00 to <1.50 mg/m^2 group, and 7 patients in the >1.50 mg/m^2 group. One of these 12 patients, (>1.00 to <1.50 mg/m^2 group was hospitalized because of Grade 2 vomiting with Grade 2 anorexia and Grade 1 abdominal pain; these events were considered by the investigator to be unrelated to study drug. Overall, 15 (35%) of 43 patients experienced thrombocytopenia (treatment-emergent platelet count decreased) during the study. Of the 15 patients who experienced thrombocytopenia, all 15 experienced at least 1 episode that was considered by the investigator to be at least possibly related to study drug. More patients in the two highest dose groups experienced thrombocytopenia (50% and 58% of patients in the >1.00 to <1.50 mg/m^2 group and > 1.50 mg/m^2 group, respectively) than in the lower dose groups (0%, 22% and 33% of patients in the 0.25 mg/m^2, 0.40 to 0.60 mg/m^2, >0.60 to 1.00 mg/m^2 dose groups, respectively). Most episodes of thrombocytopenia experienced during the study were mild or moderate (Grade 1 or 2) in intensity. Two (5%) of 43 patients, both of whom were at the 1.56 mg/m^2 level experienced Grade 3 thrombocytopenia during the study. No patient experienced Grade 4 thrombocytopenia during the study. Furthermore, no patient was reported to have received a platelet transfusion for thrombocytopenia or experienced any bleeding events associated with thrombocytopenia.

Thirteen (30%) of 43 patients experienced at least 1 episode of treatment-emergent diarrhea. An apparent dose-relationship also was seen with regard to the incidence of diarrhea, with 0 (0%) of 7 patients in the 0.25mg/m^2 group, 1 (11%) of 9 patients in the 0.40 to 0.60 mg/m^2 group, 2 (22%) of 9 patients in the >0.60 to 1.00 mg/m^2 group, 3 (50%) of 6 patients in the >1.00 to <1.50 mg/m^2 group, and 7 (58%) of 12 patients in the 1.50 mg/m^2 group experiencing at least 1 episode of treatment-emergent diarrhea during the study. Diarrhea was Grade 1 or 2 in intensity for 9 of 13 patients. Four (9%) of 43 patients experienced at least 1 episode of Grade 3 diarrhea in the study, 1 patient in the 0.40 to 0.60 mg/m^2 group and 3 patients in the 1.50 mg/m^2 group. For all 3 patients in the 1.50 mg/m^2 group, Grade 3 diarrhea occurred during Cycle 1, was considered by the investigator to be study drug-related, and, therefore, was considered to be a DLT. At least 1 episode of diarrhea was considered by the investigator to be study drug related for 10 of 13 patients, 2 patients in the >0.60 to 1.00 mg/m^2 group, 1 patient in the >1.00 to <1.50 mg/m^2 group, and 7 patients in the >1.50 mg/m^2 group. The study drug dose was reduced because of diarrhea for 1 patient (Patient No. 42; 1.50 mg/m^2); study drug was continued unchanged for the remaining 12 patients. Eight patients required treatment with loperamide for the management of diarrhea, 1 patient each in the 0.40 to 0.60 mg/m^2 and >0.60 to 1.00 mg/m^2 groups and 6 patients in the ≥1.50 mg/m^2 group.

Although an apparent trend was not seen across individual groups, the incidence of anorexia was notably higher among patients who received PS-341 at doses >1.00 mg/m^2 compared to those who received PS-341 at doses <1.00 mg/m^2, with 9 (50%) of 18 patients who received PS- 341 >1.00 mg/m^2 and 2 (8%) of 25 patients who received PS-341 <1.00 mg/m^2 experiencing treatment-emergent anorexia during the study. There was no apparent dose relationship in the reported incidences of pyrexia, dyspnea, abdominal pain, or headache.

In summary, among the 43 patients treated with PS-341 in this study, 8 (19%) experienced treatment-emergent peripheral neuropathy, 0 (0%) of 7 patients in the ≤ .025 mg/m^2 group, 1 (11%) of 9 patients in the 0.40 to 0.60 mg/m^2 group, 1 (11%) of 9 patients in the >0.60 to 1.00 mg/m^2 group, 2 (33%) of 6 patients in the >1.00 to <1.50 mg/m^2 group, and 4 (33%) of 12 patients in the 1.50 mg/m^2 group. The incidence of peripheral sensory neuropathy was higher among patients who received PS-341 at doses >1.00 mg/m^2 compared to those who received PS-341 at <1.00 mg/m^2, with 6 (33%) of 18 patients who received PS-341 >1.00 mg/m^2 and 2 (8%) of 25 patients who received PS-341 1.00 mg/m^2 experiencing treatment-emergent peripheral sensory neuropathy during the study.

The emergence of peripheral sensory neuropathy, based on whether peripheral sensory neuropathy was present at baseline (as reported in the adverse event data), is presented in the sponsor's Table 12-6, overall and by dose group.

Table 38: Onset of Peripheral Sensory Neuropathy, By Baseline Status and Dose Group

	PS-341 Dose Group (mg/m^2)					
MedDRA Preferred Term	**≤0.25 (n=7) n (%)**	**0.40 - 0.60 (n=9) n (%)**	**>0.60 – 1.00 (n=9) n (%)**	**>1.00 - <1.50 (n=6) n (%)**	**≥1.50 (n=12) n (%)**	**Total (n=43) n (%)**
Present at baseline:						
N	0	4	2	2	11	19
Resolved during study	–	1 (25)	0	0	0	1 (5)
Continued unchanged during study	–	3 (75)	1 (50)	2 (100)	7 (64)	13 (68)
Worsened during study[a]	–	0	1 (50)	0	4 (36)	5 (26)
Not present at baseline:						
N	7	5	7	4	1	24
Presented during study[a]	0	1 (20)	0	2 (50)	0	3 (13)
Not present during study	7 (100)	4 (80)	7 (100)	2 (50)	1 (100)	21 (88)

sponsor's table 12-6 protocol 98-104A

a Peripheral sensory neuropathy that presented or worsened (i.e., increased in intensity) after the start of study drug administration was considered treatment-emergent.

Overall, 19 (44%) of 43 patients had peripheral sensory neuropathy at baseline, 4 (44%) of 9 patients in the 0.40 to 0.60 mg/m^2 group, 2 (22%) of 9 patients in the >0.60 to 1.00 mg/m^2 group, 2 (33%) of 6

patients in the >1.00 to <1.50 mg/m^2 group, and 11 (92%) of 12 patients in the ≥1.50 mg/m^2 group; no patient in the ≤0.25 mg/m^2 group had peripheral neuropathy at baseline. For 17 of these 19 patients, peripheral sensory neuropathy was grade 1 at baseline; peripheral sensory neuropathy was grade 2 at baseline for 2 patients.

Peripheral sensory neuropathy remained unchanged or resolved during the study for approximately three-fourths (14 of 19 patients; 74%) of patients who had peripheral sensory neuropathy at baseline. Five (26%) of 19 patients with peripheral sensory neuropathy at baseline experienced worsening and, therefore, treatment-emergent, peripheral sensory neuropathy during the study. Of the 24 patients who did not have peripheral sensory neuropathy at baseline, 3 (13%) experienced peripheral sensory neuropathy during the study. Of the 8 patients who experienced treatment-emergent peripheral neuropathy, 6 previously had received treatment with neurotoxic chemotherapeutic agents. Furthermore, 5 of 8 patients had peripheral sensory neuropathy at baseline.

The 8 patients who experienced treatment-emergent peripheral sensory neuropathy during the study as assessed by the investigator are summarized in sponsor's table 12-7.

Table 39: Patients with Treatment-Emergent Peripheral Sensory Neuropathy

Dose (mg/m^2)	Pt. No.	Sex	Age (years)	Tumor Type	Neuropathy at Baseline (Grade)?	Prior Neurotoxic Chemotherapy[a]	Onset Cycle / Day	Grade	Relationship	Intervention Required?	Outcome
0.60	15	F	65	Lung	No	Docetaxel Vinblastine	C1, D8	2	Unrelated	No	Decreased in intensity; unresolved
0.90	23	F	52	Renal	Yes (Grade 1)	None	+LD, D25	3	Unrelated	No	Unresolved
1.08	27	M	73	Colon	No	None	+LD, D13	1	Possible	No	Resolved
1.30	31	M	64	HEENT	No	Cisplatin Paclitaxel	C2, D1	3	Definite	Yes; medication	Unresolved
1.56	33	M	50	Pancreatic	Yes (Grade 1)	Cisplatin	+LD, D11	2	Possible	None	Unresolved
	35	M	45	Lung	Yes (Grade 1)	Carboplatin Paclitaxel Docetaxel Vinblastine	C3, D4	3	Definite	None	Unresolved
	36	M	63	Colon	Yes (Grade 1)	Oxaliplatin	+LD, D6	2	Unrelated	Not reported	Unresolved
	39	F	40	Ovarian	Yes (Grade 2)	Cisplatin Carboplatin Paclitaxel	C1, D2	3	Probable	No	Resolved

sponsor's table 12-7 protocol 98-104A

Key: M=male; F=female, +LD=After last dose.

a Chemotherapeutic agents classified as neurotoxic included thalidomide, vincristine, vinblastine, cisplatin, carboplatin, oxaliplatin, docetaxel, and paclitaxel.

No patient died during study participation or within 30 days after the last study drug dose.

The following sponsor's table indicates the patients who discontinued therapy for adverse events and the investigator's assessment of causality.

Table 40: Protocol 98-104A Discontinuations Due to Adverse Events

Dose mg/m2	MeDRA term	cycle at onset	grade	relation
.6	Fatigue	1	2	Unrelated
1.3	Peripheral sensory neuropathy	2	3	Definite
1.56	Myocardial ischemia	1	2	Possible
1.56	Small intestinal obstruction	1	3	Unrelated
1.56	Peripheral neuropathy	3	2	Definite
	Peripheral sensory neuropathy	3	3	Definite
1.56	Dehydration	1	2	Possible
	Nausea	1	2	Possible
	Vomiting	1	2	Possible
1.56	Dyspnea	2	3	Unrelated
	Fatigue	2	3	Unrelated
	Hypotension	2	2	Unrelated

sponsor's table 14.3.2.3

There were 31 patients in whom 26S proteasome inhibition data were obtained. Among these 31 patients, maximum inhibition of 26S proteasome activity was <70% for 10 patients, between 70 to 80% for 15 patients, and ≥80% for 6 patients. The incidence of DLTs, Grade 3 adverse events, serious adverse events, and adverse events leading to study drug discontinuation was higher among patients with maximum inhibition of 26S proteasome activity ≥80% compared to patients with maximum inhibition <80%. However, the 90% confidence limits around the proportions were broad because of the small sample size.

The maximally tolerated dose of PS-341 when administered twice weekly for 2 weeks (on days 1, 4, 8, and 11) followed by a 10-day rest period was determined to be 1.30 mg/m^2. Dose limiting toxicities experienced in this study, all by patients at the 1.56 mg/m^2 dose level, included grade 3 diarrhea (3 patients) and grade 3 peripheral sensory neuropathy (1 patient). The majority of patients (40 of 43 patients; 93%) received a complete treatment cycle (4 of 4 PS-341 doses) in Cycle 1. Approximately half (24 of 43 patients; 56%) received at least 2 complete treatment cycles (8 of 8 PS-341 doses) in this study; 86%, 44%, 89%, 50%, and 25% of patients in the

<0.40 mg/m^2, 0.40 to 0.60 mg/m^2, >0.60 to 1.00 mg/m^2, >1.00 to <1.50 mg/m^2, and ≥1.50 mg/m^2 groups, respectively.

All (100%) 43 patients experienced at least 1 treatment-emergent adverse event during the study. Among all 43 patients, the most commonly reported adverse events were anemia (79%), fatigue (65%), constipation (44%), nausea (44%), and thrombocytopenia (35%).

Studies LCCC9834/00-31 and M34100-027

Study LCCC9834/00-31 was a phase I dose-escalation examination of DLT, MTD and PD of VELCADE administered as a twice weekly for four consecutive weeks IV bolus to patients with advanced, refractory hematologic malignancies. Dose levels were 0.4, 1.04, 1.2, and 1.38 mg/m^2. Study M34100-027 was a phase I dose-escalation study of VELCADE in combination with gemcitabine for patients with advanced solid tumors. The VELCADE was given twice weekly for two weeks every 21 days. These studies have been reviewed for any unique safety issues. None have been identified. Since the sponsor has requested the indication for single agent VELCADE for patients with advanced, refractory MM, these two studies are not reviewed in further detail herein.

Sponsor's table summarizes the dose limiting toxicities encountered in the phase 1 studies and maximally tolerated doses on each schedule.

Table 41 Overview of Dose, Regimen, DLT and MTD in the phase 1 PS-341 Studies

Protocol Number Patient Population	PS-341 Dose (mg/m^2)	Dosing Regimen	MTD (mg/m^2)	Dose Limiting Toxicity
Study DM98-194: Solid tumor N=53	0.13 –2.0	1x per week for 4 weeks (Days 1, 8, 15, and 22)	1.6	Diarrhea, hypotension (including orthostatic hypotension), tachycardia, vision abnormal NOS, and syncope
Study 98-104A: Solid tumor N=43	0.13 –1.56	2x per week for 2 weeks, (Days 1, 4, 8, and 11)	1.3	Diarrhea, peripheral sensory neuropathy
Study LCCC 9834 / 00-31:[b] Hematologic malignancies N=27	0.4 –1.38	2x per week for 4 weeks, (Days 1, 4, 8, 11, 15, 18, 22, and 25)	1.04	Hyponatremia, hypokalemia, malaise

Source: Table 2.7.2-12 Clinical Study Report DM98-194, Clinical Study Report 98-104A, and Clinical Study Report LCCC9834/00-31.
a Maximum number of cycles administered to a single patient during that study.
b Results from these 2 studies were presented in 1 clinical study report

Study M34100-024

Study M34100-024 was a phase II prospective, randomized, multicenter study conducted at MM centers in the US designed to evaluate the efficacy and safety of PS-341 administered at doses of

1.0 and 1.3 mg/m^2 given alone, or in combination with dexamethasone subsequent to inadequate response to PS-341 monotherapy, administered to patients with MM who had failed to respond to or had relapsed following either conventional or high-dose front-line therapy. A treatment cycle was comprised of four injections of PS-341 (on Days 1, 4, 8, and 11) followed by a 10-day rest period; a maximum of up to 8 cycles of treatment could be administered. Patients who were, in the investigator's opinion, benefiting from PS-341 treatment in the current study were eligible to continue PS-341 treatment in an extension study (M34101-029) outside the auspices of this protocol.

During the first 2 treatment cycles, all patients were to receive PS-341 at doses of 1.0 or 1.3 mg/m^2, based on random assignment. Thereafter, dexamethasone may have been added to the patient's treatment regimen, for patients with a suboptimal response to PS-341 alone. Patients who received dexamethasone in combination with PS-341 were to take dexamethasone 20 mg by mouth (PO) 4 times per week (on Monday, Tuesday, Thursday, and Friday) on each day of and day after PS-341 administration for 2 consecutive weeks (Days 1, 2, 4, 5, 8, 9, 11, and 12). Thus, for every dose of PS-341 1.3 mg/m^2, patients were to receive a total of 40 mg of dexamethasone. This safety review discusses the safety profile of VELCADE alone and does not review the safety of the combination of VELCADE plus dexamethasone.

The amount (in mg) of PS-341 to be administered was to be determined based on body surface area (BSA), which was to be calculated based on body weight using a standard nomogram. The dose was to be calculated on Day 1 of each cycle; the dose administered was to remain the same throughout each cycle but was to be recalculated at the start of the next cycle. If a patient experienced a notable change in weight (i.e., .8 lbs or 3.6 kg) within a cycle, as determined by an unscheduled weight assessment, then the patient's dose was to be recalculated at that time. Per protocol, patients who experienced PD after receiving PS-341 alone in Cycles 1 and 2, or PD or NC after receiving PS-341 alone in Cycles 3 and 4 vs last assessment, or Cycles 5 and 6 vs last assessment were to start treatment with dexamethasone in combination with PS-341. For all patients switching to combination therapy, the dosing regimen of PS-341 was to be continued unchanged and 20 mg dexamethasone was to be administered on each day of and day after PS-341; for a total of 40 mg dexamethasone with each PS-341 dose.

Dose escalation was not allowed for any patient. Before each study drug dose, the patient was to be evaluated for possible toxicities that occurred after the previous dose(s). Toxicities were to be assessed according to the NCI Common Toxicity Criteria (CTC), Version 2.0.
Previously established or new toxicities observed any time were to be managed as follows:

- If the patient experienced febrile neutropenia, a Grade 4 hematologic toxicity, with the exception of lymphopenia, or any Grade 3 non-hematologic toxicity considered by the investigator to be related to study drug, then study drug was to be held.
- For non-hematologic toxicities, study drug was to be held for up to 2 weeks until the toxicity returned to Grade 1 or better.
- For hematologic toxicities, with the exception of lymphopenia, study drug was to be held for up to 2 weeks until the patient had a hemoglobin value ≥8 g/dL, an ANC ≥1.0 X 109/L, and a platelet count ≥30 X 109/L.

• Dose interruption or study discontinuation was not required for lymphopenia.
• If, after study drug was held, the toxicity did not resolve, as defined above, then the patient was to be discontinued from the study.
• If the toxicity resolved, as defined above, then PS-341 could have been restarted at a reduced dose, as follows:
• If the patient was receiving 1.3 mg/m2, the dose was to be reduced to 1.0 mg/m2.
• If the patient was receiving 1.0 mg/m2, the dose was to be reduced to 0.7 mg/m2.
• If the patient was receiving 0.7 mg/m2, the patient was to be discontinued from the study. Dose reduction below 0.7 mg/m2 was not allowed.

If a patient had a creatinine clearance <30 mL/minute, then the PS-341 dose could have been modified based on proteasome inhibition data collected at 1 hour post-dose. The level of 26S proteasome activity inhibition should have been >65% and <80%. If inhibition of 26S proteasome activity was 65% or lower or 80% or higher, then the PS-341 dose was to be modified accordingly.

Dose interruptions or modifications were not to be made for dexamethasone.
If the drug was held for more than 2 weeks or a patient missed 3 weeks of a cycle then the patient was removed from study. If a patient was determined to have toxicities indicative of clinical deterioration and/or disease progression, then the patient was to be discontinued from the study.

The study design planned for 64 patients; 54 patients were enrolled and treated including 28 patients treated at 1.0 mg/m^2 and 26 patients treated at 1.3 mg/m^2.

The inclusion/exclusion criteria have been summarized above (section VI-3).

Safety assessments performed during treatment included monitoring for adverse events (AEs), including a directed questionnaire for neurologic toxicities (FACT/GOG-Ntx questionnaire); vital signs before and following each PS-341 dose; review of concomitant medications and other therapies, including growth factors and transfusions; clinical laboratory tests, including hematology, clinical chemistry, electrolytes, glucose, amylase, total protein, albumin, urinalysis, and interleukin-6 (IL-6); and administration of the QOL instrument.

The pharmacokinetic data derived from this study were limited to 4 patients with 2-hour profiles, and to 16 patients with sparse samples originally intended for population pharmacokinetic analysis. In spite of the limitations, the initial pharmacokinetic profile of PS-351 confirms the rapid decrease in plasma PS-341 levels over the first 30 minutes following administration in all patients, which is consistent with previous observations in a Phase 1 trial (Study DM98-194). The terminal elimination rate of PS-341 could not be established due to lack of sample collection after 2 hours from administration. Plasma levels of PS-341 24 hours after dosing, or 1-3 hours

before subsequent doses of PS-341 were either undetectable or just above the limit of quantification of 0.5 ng/mL.

Pharmacodynamic assessment using the ———————— assay was conducted in only 26 patients. Most observations are derived from Cycle 1, Day 1 (n = 25) and Cycle 1, Day 11 (n = 24); data for Cycle 7 is limited to few observations (n = 8 to 11 at various time points). A dose-dependent increase of average maximum proteasome inhibition was observed in Cycle 1; this trend was not observed in Cycle 7, possibly due to the very low number of observations, especially at the 1.3 mg/m^2 dose (n = 2 to 3). A dose-dependent decrease in the number of patients with levels of proteasome inhibition <50% was also observed, with 8 patients at 1.0 mg/m^2 dose and only 1 at 1.3 mg/m^2 dose having these low levels. Average levels of maximum proteasome inhibition were similar to those observed in Phase 1 and 2 studies at the same dose regimen. In 4 patients, additional samples for proteasome inhibition were obtained over 24 hours post-dose. The time course of 26S proteasome inhibition over 24 hours from administration observed in these patients was similar to that reported in previous Phase 1 and 2 studies.

All 54 patients (100%) experienced at least 1 treatment-emergent adverse event during the study. Overall, the most commonly reported adverse events were fatigue (70%), nausea (54%), diarrhea (44%), pyrexia (41%), constipation (37%), peripheral neuropathy NOS (37%), arthralgia (35%), insomnia (35%), headache (31%), limb pain (31%), thrombocytopenia (30%), and upper respiratory tract infection (30%). Thirty-nine (72%) of 54 patients experienced at least 1 treatment-emergent adverse event of Grade 3 intensity including 68% and 77% of patients in the 1.0 and 1.3 mg/m^2 dose groups, respectively. Commonly reported Grade 3 adverse events included thrombocytopenia (12 patients; 22%), neutropenia (9 patients; 17%), lymphopenia (6 patients, 11%), and peripheral neuropathy NOS (5 patients; 9%). The incidence of Grade 4 events was 9% (5 of 54 patients) and included 1 report each of aortic aneurysm, peripheral neuropathy NOS, large intestinal perforation, hypercalcemia, and thrombocytopenia. A review of the incidence of the most commonly reported adverse events across the 2 dose groups for those events with a >20% higher incidence in the higher dose group as compared to the lower dose group was conducted to evaluate for a possible dose effect.

Adverse events reported more frequently in the 1.3 mg/m^2 dose group (>20% difference in incidence rates) included diarrhea (65% for the 1.3 mg/m^2 dose group compared to 25% in the 1.0 mg/m^2 dose group), peripheral neuropathy NOS (58% compared to 18%), vomiting (38% compared to 14%), anxiety (35% compared to 14%), and night sweats (23% compared to 0%). Interestingly, arthralgia and peripheral edema were reported with a higher incidence (>20% difference) in the 1.0 mg/m^2 dose group as compared to the 1.3 mg/m^2 dose group. Overall, adverse events were most frequently reported in the general disorders and administrative site conditions SOC, reported in 86% and 96% of patients in the 1.0 and 1.3 mg/m^2 dose groups, respectively. The most commonly reported adverse events in this SOC included fatigue (70%), pyrexia (41%), weakness (28%), and malaise (17%). Most events reported in this SOC were mild or moderate in severity and did not limit PS-341 administration. Adverse events of Grade 3 intensity included fatigue and weakness (4 patients each; 7%), and pyrexia and rigors (2 patients each; 4%). Overall, only 3 (6%) patients discontinued PS-341 because of a general disorder or administration site condition. Forty-six (85%) of the 54 patients experienced at least 1 treatment

adverse event in the gastrointestinal disorders SOC, including 82% of patients in the 1.0 mg/m^2 dose group and 88% in the 1.3 mg/mg2 dose group. The most commonly reported gastrointestinal events included nausea (54%), diarrhea (44%), constipation (37%), vomiting (26%), and dyspepsia (17%). Four patients experienced a treatment-emergent gastrointestinal disorders of Grade 3 (3 patients) or Grade 4 (1 patient) intensity. No patient discontinued treatment with PS-341 because of a gastrointestinal disorder.

The overall incidence of peripheral neuropathy (including peripheral neuropathy NOS and peripheral sensory neuropathy) was 41%, including 21% of patients in the 1.0 mg/m^2 group and 62% of patients in the 1.3 mg/m^2 group. Peripheral neuropathy was ≥ grade 3 in intensity for 6 (11%) patients overall, 2 (7%) of 28 patients in the 1.0 mg/m^2 group and 4 (15%) of 26 patients in the 1.3 mg/m^2 group. In one of these patients, who had Grade 3 neuropathy at baseline, Grade 4 peripheral neuropathy was reported on study. PS-341 dosing was held for peripheral neuropathy in 2 (4%) patients, and the dose was reduced for 6 (11%) patients. PS-341 was permanently discontinued because of peripheral neuropathy for 5 (9%) patients, including 1 patient in the 1.0 mg/m^2 group and 4 patients in the 1.3 mg/m^2 group. Only 1 (8%) of 12 patients with no symptoms of peripheral neuropathy reported at baseline on the FACT/GOG-Ntx questionnaire experienced Grade 3 peripheral neuropathy on study.

Overall, 56% of patients (30 of 54), including 46% in the 1.0 mg/m^2 dose group and 65% patients in the 1.3 mg/m^2 dose group had at least 1 hematologic abnormality reported as an adverse event. Commonly reported hematologic adverse events included thrombocytopenia (30%), anemia (20%), neutropenia (19%), and lymphopenia (13%). Grade 3 hematologic adverse events were reported with a similar incidence across the dose groups (43% and 46% in the 1.0 and 1.3 mg/m^2 dose groups, respectively). Thrombocytopenia was reported as an adverse event for 32% and 27% of patients in the 1.0 and 1.3 mg/m^2 dose groups, respectively; in 29% and 15% of patients, respectively, Grade 3 thrombocytopenia was reported. In 1 patient (1.3 mg/m^2) Grade 4 thrombocytopenia was reported. No serious bleeding events associated with thrombocytopenia were reported during the study. Five patients had doses held for thrombocytopenia, and only 1 (2%) patient discontinued the study due to thrombocytopenia. The reported patient incidence of serious adverse events was similar between the 1.0 mg/m^2 dose group (39%) and the 1.3 mg/m^2 dose groups (42%). The most commonly reported serious adverse events were pneumonia (11%), pyrexia (9%), peripheral neuropathy (6%), upper respiratory tract infection (4%), syncope (4%), and dyspnea (4%).

One patient died on study, i.e., within 20 days of the last dose of PS-341; the primary cause of death, reported as pneumonia, was considered unrelated to study treatment by the investigator. Additionally, 7 patient deaths were reported more than 20 days after the last dose of study drug. Six of these 7 patients were reported to have died of progression of myeloma and for 1 patient multisystem organ failure was reported as the cause of death.

Overall, 13 (24%) of 54 patients discontinued study drug because of an adverse event, including 11% of patients in the 1.0 mg/m^2 dose group and 38% of patients in the 1.3 mg/m^2 dose group. The most commonly reported adverse events leading to study drug discontinuation were peripheral neuropathy (5 patients, 9%) and pneumonia (2 patients, 4%). PS-341 did not appear to

be associated with hepatic, renal, CNS, or direct cardiac toxicities, as determined by review of adverse event and laboratory data.

Study M34100-025

Study Objectives:

The primary objective of this study was to determine the overall response rate [the combined complete response (CR) + partial response (PR) + minimal response (MR) rates] following treatment with monotherapy PS-341 1.3 mg/m^2/dose in patients with MM who had relapsed following initial front-line therapy and were refractory to their most recent therapy.

This was a phase II open-label, multi-center study designed to evaluate the efficacy and safety of PS-341 at a dose of 1.3 mg/m^2 given alone, or in combination with dexamethasone subsequent to inadequate response to PS-341 monotherapy. A treatment cycle was comprised of four injections of PS-341 (on Days 1, 4, 8, and 11) followed by a 10-day rest period; a maximum of up to 8 cycles of treatment could be administered. Patients who were, in the investigator's opinion, benefiting from PS-341 treatment in the current study were eligible to continue PS-341 treatment in an extension study (M34101-029) separate from this protocol.

Patient eligibility was assessed during screening within 14 days before the first drug dose. Eligible patients initiated treatment with PS-341 on Day 1, Cycle 1. During each treatment cycle, PS-341 was to be administered twice per week (e.g., Monday and Thursday) for 2 weeks (Days 1, 4, 8, and 11) followed by a 10-day rest period, making each treatment cycle 21 days (3 weeks). During treatment, patients were to attend study center visits on each day of PS-341 administration as well as once between Days 15 and 18, inclusive, of the rest period of Cycles 2, 4, and 6.
During the first 2 treatment cycles, all patients were to receive PS-341 1.3 mg/m^2. Thereafter, dexamethasone may have been added to the patient's treatment regimen, for patients with a suboptimal response to PS-341 alone. Patients who received dexamethasone in combination with PS-341 were to take dexamethasone 20 mg by mouth (PO) 4 times per week (on Monday, Tuesday, Thursday, and Friday) on each day of and day after PS-341 administration for 2 consecutive weeks (Days 1, 2, 4, 5, 8, 9, 11, and 12). Thus, for every dose of PS-341 1.3 mg/m^2, patients were to receive a total of 40 mg of dexamethasone. This safety review discusses the use of VELCADE alone.

A total of up to 200 patients were to be enrolled in this study including 75 patients planned in the original protocol (designated Cohort 1) plus an additional cohort of up to 125 patients added by protocol amendment (designated Cohort 2). Two hundred fourteen (214) patients provided written informed consent to participate in this study, of whom 202 were enrolled and received at least one dose of PS-341. Of these 202 patients, 78 were enrolled into Cohort 1 and 124 were enrolled into Cohort 2.

Criteria for Inclusion/Exclusion: See section VI-3.

Treatment: See section VI-3 also.

Patients were to receive a maximum of eight 3-week treatment cycles; therefore, the maximum duration of treatment in this study was 24 weeks (~6 months). The actual number of cycles administered for each patient was based on the response to therapy.

There was to be at least 72 hours between each dose of PS-341. Patients were to be observed at the clinical site for a minimum of 2 hours after completion of study drug administration. The patient was to be considered clinically stable by the investigator before discharge.

The amount (in mg) of PS-341 to be administered was to be determined based on body surface area (BSA). BSA was to be calculated based on height and body weight using a standard nomogram. No dose adjustment was to be made for obese patients. The dose was to be calculated on Day 1 of each cycle; the dose administered was to remain the same throughout each cycle but was to be recalculated at the start of the next cycle. If a patient experienced a notable change in weight (e.g., loss or gain of 8 lbs) within a cycle, as determined by an unscheduled weight assessment, then the patient's dose was to be recalculated at that time.

Dose escalation was not allowed in any patient. Before each study drug dose, the patient was to be evaluated for possible toxicities that may have occurred after the previous dose(s). Toxicities were to be assessed according to the NCI Common Toxicity Criteria (CTC), Version 2.0. Previously established or new toxicities observed at any time were to be managed as follows:

- If the patient experienced febrile neutropenia, a grade 4 hematologic toxicity, with the exception of lymphopenia, or any ≥ Grade 3 non-hematologic toxicity considered by the investigator to be related to study drug, then study drug was to be held.
- For non-hematologic toxicities, study drug was to be held for up to 2 weeks until the toxicity returned to Grade 1 or better.
- For hematologic toxicities, with the exception of lymphopenia, study drug was to be held for up to 2 weeks until the patient had a hemoglobin value ≥8 g/dL, an absolute neutrophil count (ANC) ≥1.0 X 10⁹/L, and a platelet count ≥30 X 10⁹/L.
- Dose interruption or study discontinuation was not required for lymphopenia.
- If, after study drug was held, the toxicity did not resolve, as defined above, then PS-341 was to be discontinued.
- If the toxicity resolved, as defined above, then PS-341 may have been restarted at a reduced dose, as follows:
    - If the patient was receiving 1.3 mg/m2, the dose was to be reduced to 1.0 mg/m2.
    - If the patient was receiving 1.0 mg/m2, the dose was to be reduced to 0.7 mg/m2.
    - If the patient was receiving 0.7 mg/m2, then PS-341 was to be discontinued. Dose reduction below 0.7 mg/m2 was not allowed.

If a patient had a creatinine clearance <30 mL/minute, then the PS-341 dose may have been modified based on proteasome inhibition data collected at 1 hour post-dose. The level of 26S proteasome activity inhibition was to be >65 and <80%. If inhibition of 26S proteasome

activity was 65% or lower or 80% or higher, then the PS-341 dose was to be modified accordingly.

Dose interruptions or modifications were not to be made for dexamethasone. If a patient was determined to have toxicities indicative of clinical deterioration and/or disease progression, then PS-341 was to be discontinued.

Results:

Safety assessments performed during treatment included monitoring for adverse events, including a directed questionnaire for neurologic toxicities (FACT/GOG-Ntx questionnaire); vital signs before and following each PS-341 dose; review of concomitant medications and other therapies, including growth factors and transfusions; clinical laboratory tests, including hematology, clinical chemistry, electrolytes, glucose, amylase, total protein, albumin, urinalysis, and interleukin-6 (IL-6); and administration of the QOL instrument.

All 202 patients experienced at least 1 treatment-emergent adverse event in this study. Overall, the most commonly reported adverse events were nausea (64%), diarrhea and fatigue (49% each), thrombocytopenia (44%), constipation (43%), vomiting (36%), anorexia (34%), pyrexia (34%) peripheral neuropathy, including sensory and peripheral neuropathy aggravated (34%), and anemia (31%). Approximately two-thirds (68%) of patients experienced at least 1 Grade 3 adverse event. Although the incidence of Grade 3 adverse events overall was 68%, the incidence of particular Grade 3 adverse events was relatively low. Grade 3 adverse events occurring at an incidence >10% included thrombocytopenia (28%), peripheral neuropathy, including sensory and peripheral neuropathy aggravated (12%), fatigue (12%), and neutropenia (11%). Overall, the incidence of Grade 4 adverse events was 14%. The most commonly reported Grade 4 adverse events included thrombocytopenia and neutropenia, each of which was reported for 3% of patients. All other grade 4 adverse events reported occurred at an incidence of ≤1%.

Overall, adverse events were most frequently reported in the gastrointestinal disorders SOC, with 89% of patients experiencing at least 1 adverse event in this SOC. Commonly reported gastrointestinal events included nausea (64%), diarrhea (49%), constipation (43%), and vomiting (36%). Most of the gastrointestinal events were mild or moderate in intensity, were manageable with supportive therapies (e.g., antiemetics, antipropulsives), and did not limit PS-341 administration. Six percent (6%) of patients discontinued PS-341 because of a gastrointestinal events. Gastrointestinal events were Grade 3 in intensity for 19% of patients and were Grade 4 in (2%).

A total of 34% of patients experienced treatment-emergent peripheral neuropathy, including reports of peripheral sensory neuropathy and peripheral neuropathy aggravated. Peripheral neuropathy was study drug-related for 31% of patients and Grade 3 in intensity for 12% of patients. No grade 4 peripheral neuropathy was reported. The majority of these patients required treatment for their symptoms. Furthermore, 12% of patients required at least 1 PS-341 dose reduction and 4% of patients discontinued PS-341 because of peripheral neuropathy. Reversibility of peripheral neuropathy was seen in a small proportion of patients (10 of 68 patients; 15%); however, limited follow-up data regarding the outcome of peripheral neuropathy

are available. Only 1 (3%) of 33 patients without symptoms reported on the FACT/GOG-Ntx questionnaire at baseline related to peripheral neuropathy experienced grade 3 peripheral neuropathy on study compared to 26 (16%) of 158 patients with symptoms reported at baseline. More than half (51 of 94 patients, 54%) of the patients with peripheral neuropathy or symptoms of peripheral neuropathy required treatment for their symptoms of neuropathy. Treatments commonly administered included gabapentin, vitamin and nutritional supplements, opioids (e.g., oxycodone, hydrocodone, fentanyl, morphine), antidepressants (e.g., amitriptyline, nortriptyline, desipramine), and non-steroidal anti-inflammatory agents (e.g., celecoxib, rofecoxib, ibuprofen).

Patients with peripheral neuropathy or symptoms of peripheral neuropathy commonly reported other musculoskeletal and connective tissue disorders during the study, including arthralgia (32 patients), pain in limb (28 patients), bone pain/bone pain aggravated (19 patients), back pain/back pain aggravated and muscle cramps (18 patients each), myalgia (15 patients), and muscle spasm (8 patients).

Nineteen patients with peripheral neuropathy or symptoms of peripheral neuropathy had electromyography (EMG) and/or nerve conduction studies (NCS) and quantitative sensory testing (QST). Findings of these special studies revealed that the clinical and electrophysiologic characteristics of the neuropathy were consistent with a length-dependent sensory axonal polyneuropathy with predominant small fiber involvement.

Orthostatic/postural hypotension was reported for 11 (5%) of patients. Orthostatic / postural hypotension was mild or moderate in intensity for the majority (7 of 11 patients) of patients. Four (2%) patients experienced orthostatic/postural hypotension of grade 3 intensity during the study; no episodes of Grade 4 orthostatic/postural hypotension were reported. Hypotension was reported as a serious adverse event for 4 (2%) patients. Two of these 4 patients discontinued VELCADE because of orthostatic/postural hypotension; for both patients, this event was considered to be study drug-related. Of the 11 patients who experienced treatment-emergent orthostatic / postural hypotension, none were determined to have orthostatic hypotension via neurologic examination at screening, as defined by a decrease from supine to standing in systolic or diastolic blood pressure of >20 mmHg or >10 mmHg, respectively. Of these 11 patients, 5 were reported to have hypertension / elevated blood pressure at baseline. Four of these 5 patients were receiving medication for the management of hypertension, including metoprolol, atenolol, quinapril, and diltiazem. Additionally, 1 of these 5 patients was receiving warfarin and digoxin for the management of atrial fibrillation. Mean systolic blood pressure, diastolic blood pressure, and pulse decreased from pre-dose to both post-dose time points on Day 1. In the entire patient group, the mean changes in blood pressure and pulse from pre-dose on Cycle 1, Day 1 to 1 and 2 hours post-dose were small and not clinically significant. The mean changes for blood pressure were $\leq$ -2.4 mmHg and for pulse $\leq$-1.1 beats/minute. Similar results were noted following dosing on Cycle 1 Day 11; insignificant small mean decreases from pre-dose to both post-dose time points were noted for systolic and diastolic blood pressure.

Other vascular or cardiac events were ongoing at baseline for 4 additional patients, including systolic murmur and atrial enlargement, deep vein thrombosis, bradycardia and organic heart disease, and borderline left atrial abnormality / left ventricular hypertrophy. Three patients

experienced orthostatic/postural hypotension concurrent with peripheral neuropathy or symptoms of peripheral neuropathy (per the sponsor's assessment). Additionally, 1 patient each experienced orthostatic/postural hypotension immediately before the onset of or shortly after the resolution of peripheral neuropathy. Furthermore, orthostatic / postural hypotension occurred concurrently with syncope for 3 patients and with dehydration for 2 patients. Eight of 11 patients required treatment for the management of orthostatic / postural hypotension. Treatments administered included rehydration with normal saline and fludrocortisone acetate.

The incidence of embolism of any type was low, with embolism of any type being reported as an adverse event for 4 (2%) patients. Of these 4 patients, pulmonary embolism was reported for 3 (1%) patients and peripheral embolism was reported for 1 (<1%) patient. It is of note that for 2 of the 3 patients who had pulmonary embolism reported as an adverse event, the investigator reported the event as grade 1 "possible pulmonary embolism"; for both patients, possible pulmonary embolism was considered unlikely related to study drug. For the remaining patient, pulmonary embolism was assessed as Grade 3 in intensity and study drug-related. Another Patient who completed the study through Cycle 8, experienced a pulmonary embolism 4 days after his last dose of PS-341 on Day 11, Cycle 8. Pulmonary embolism was reported as a serious adverse event for this patient.

Overall, 56 (28%) patients experienced at least 1 treatment-emergent adverse event in the eye disorders SOC. Although the overall incidence of eye disorders was >10%, no particular adverse event within this SOC occurred at an incidence of 10%. Twenty-three (11%) patients experienced at least 1 eye disorder that was considered to be study drug-related. The incidence of Grade 3 eye disorders was low, with 4 (2%) patients experiencing at least 1 Grade 3 adverse event within this SOC. Eye disorders of Grade 3 intensity included diplopia, eye swelling, eyelid ptosis, and vision blurred, each of which was reported for 1 patient (<1%). No eye disorders of Grade 4 intensity were reported. Four patients (2%) experienced Grade 3 eye disorders; in one patient the event was assessed as drug related. This patient, who had no history of eye disorder at baseline, experienced the first onset of bilateral eye swelling (grade 1) on Day 9, Cycle 3, concurrent with Grade 1 left eye erythema (investigator term: increase in skin temperature around the eyes); Grade 1 bilateral blurred vision was also reported at that time. Erythema resolved by 2 weeks after onset; eye swelling and blurred vision were continuing at that time. On Day 7, Cycle 4, the patient experienced increased lacrimation and eye irritation, described as burning, which were both Grade 1 in intensity. On Day 6, Cycle 5, the burning resolved. However, at that time, the patient developed Grade 1 bilateral periorbital edema. Six days later (Day 12, Cycle 5), the patient's eyes became swollen shut; eye swelling was considered to be Grade 3 in intensity. Grade 3 eye swelling resolved the day after onset (Day 13, Cycle 5) following treatment with diphenhydramine. Study drug was not interrupted or discontinued for any of these events, all of which were assessed by the investigator as drug-related. Periorbital edema continued with resolution reported during Cycle 7. The dose was reduced for this event during Cycle 8.

Reviewer's comment: An allergic reaction seems likely.

Hematologic toxicities, primarily thrombocytopenia, were reported in 67% of patients as an adverse event, including reports of thrombocytopenia (44%), anemia (31%), and neutropenia (22%). Hematologic adverse events were Grade 3 in intensity for 39% of patients. The incidence of Grade 4 hematologic adverse events was low (5%). Thrombocytopenia was reported as an adverse event for 44% of patients and was reported as Grade 3 in intensity for 3%. Of the 6 patients who had Grade 4 thrombocytopenia, 5 had thrombocytopenia at baseline. Review of laboratory data shifts from baseline to worst value on study revealed a higher incidence of grade 3 and 4 thrombocytopenia (41% and 6%, respectively). No serious bleeding events were associated with grade 4 thrombocytopenia and no bleeding deaths occurred in this study.

Overall, half (50%) of patients experienced at least 1 serious adverse event during the study. Serious adverse events of grade 4 in intensity were reported for 13% of patients. The most common type of grade 4 serious adverse events reported during the study was related to organ arrest and/or organ system failure (i.e., cardiac, cardiopulmonary, and respiratory arrest and cardiopulmonary, congestive cardiac, pulmonary, renal, and respiratory failure), which was reported for 8 patients.

A total of 11 patients (5%) died within 20 days after the last study drug dose or died of a cause considered to be study drug-related at any time after the last study drug dose. The cause of death was assessed as study drug-related for 2 (<1%) patients, and included cardiopulmonary arrest and respiratory arrest. In the other nine, progressive disease was at least contributory. Additionally, 55 patients died in the post-study period; for all 55 patients, the cause of death was considered to be unrelated to study drug according to the investigator.

Dose Modifications:

There are three forms of dose modification available to investigators in this protocol. They include: permanent discontinuation of the drug, withholding of one or more doses of the drug, or reduction in administered dose of the drug.

In study –025, 58 of the 202 patients (29%) discontinued VELCADE, most commonly for (MedRDA) nervous system disorder, neuropathy (see sponsor's table below) . This table does not include dose reductions or doses omitted.

Table 42: Adverse Events Leading to Study Drug Discontinuation with an Incidence ≥ 1% Overall and by Relationship to Study Drug (All Patients Treated; N=202)

	All PS-341 Treated Patients (N=202)	
	Total	Study Drug-Related
MedDRA SOC - Preferred Term	n (%)	n (%)
At least 1 adverse event leading to discontinuation	58 (29)	36 (18)
Nervous system disorders	15 (7)	13 (6)
Peripheral neuropathy	7 (3)	6 (3)
Syncope	4 (2)	2 (1)
General disorders and administration site conditions	13 (6)	6 (3)
Disease progression	6 (3)	0
Fatigue	5 (2)	4 (2)
Gastrointestinal disorders	12 (6)	9 (4)
Diarrhea	6 (3)	5 (2)
Blood and lymphatic system disorders	11 (5)	8 (4)
Thrombocytopenia	8 (4)	8 (4)
Metabolism and nutrition disorders	8 (4)	5 (2)
Dehydration	4 (2)	2 (1)
Respiratory, thoracic, and mediastinal disorders	4 (2)	1 (<1)
Dyspnea	3 (1)	1 (<1)

Source: sponsor's table 12-22 clinical summary report M34100-025

The FDA reviewer's compilation of dose modifications consisting of omission of a dose or reduction of a dose is summarized below.

Table 43: Reviewer's table: Dose Modification: Omission or Reduction of Dose -025 study

	Dose Omitted n (%)	Dose Reduced n (%)
total number of patients with event	130 (64%)	68 (34%)
ADVERSE EVENTS:		
thrombocytopenia	35 (17)	9 (4)
neutropenia	28 (14)	6 (3)
peripheral neuropathy	17 (8)	25 (12)
nausea	17 (8)	8 (4)
vomiting	14 (7)	8 (4)
diarrhea	8 (4)	5 (2)
fatigue	13 (6)	12 (6)
pyrexia	11 (5)	--
SERIOUS ADVERSE EVENTS:		
pneumonia	7 (3)	--
dehydration	6 (3)	--
nausea	6 (3)	--
vomiting	5 (2)	2 (1)
pyrexia	4 (2)	--
diarrhea	3 (1)	--

(< 1%) signified by: --

The following sponsor's tables summarize toxicity observed in study –025.

Table 44: Treatment-Emergent Adverse Events Reported by ≥ 10% of Patients Overall, by MedDRA Preferred Term

MedDRA Preferred Term	n (%)
At least 1 adverse event	202 (100)
Nausea	129 (64)
Diarrhea	99 (49)
Fatigue	99 (49)
Thrombocytopenia	89 (44)
Constipation	86 (43)
Vomiting	72 (36)
Anorexia	69 (34)
Pyrexia	69 (34)
Anemia	63 (31)
Arthralgia	54 (27)
Headache	54 (27)
Insomnia	54 (27)
Peripheral neuropathy	53 (26)
Pain in limb	49 (24)
Dyspnea	45 (22)
Neutropenia	45 (22)
Rash	42 (21)
Dizziness (excl. vertigo)	39 (19)
Dehydration	38 (19)
Weakness	36 (18)
Upper respiratory tract infection	34 (17)
Cough	31 (15)
Bone pain	28 (14)
Appetite decreased	27 (13)
Back pain	27 (13)
Muscle cramps	26 (13)
Abdominal pain	25 (12)
Dysgeusia	25 (12)
Myalgia	25 (12)
Edema, peripheral	24 (12)
Rigors	24 (12)
Anxiety	23 (11)
Dyspepsia	23 (11)
Edema, lower limb	23 (11)
Weight decreased	23 (11)
Herpes zoster	22 (11)
Paresthesia	22 (11)

Source: Sponsor's table 12-3 clinical summary for protocol M34100-025

Table 45: Incidence and Prevalence of the Ten Most Commonly Reported Adverse Events, by Treatment Cycle (All Patients Treated; N=202) Number of Events per 100 Patient Doses / Treatment Cycle

Event/ Category	Cycle 1 N=749	Cycle 2 N=647	Cycle 3 N=545	Cycle 4 N=468	Cycle 5 N=400	Cycle 6 N=275	Cycle 7 N=322	Cycle 8 N=301
Nausea								
Incidence	9.9	9.0	5.7	4.7	3.5	2.4	1.2	0.3
Prevalence	10.4	13.8	12.1	11.5	11.8	9.3	8.4	7.0
Diarrhea NOS								
Incidence	8.0	6.6	5.7	3.8	3.5	2.7	1.9	1.0
Prevalence	8.4	9.3	9.9	8.1	7.8	6.4	6.8	5.6
Fatigue								
Incidence	6.4	6.5	4.8	4.5	4.0	2.9	4.3	2.7
Prevalence	6.7	12.1	13.0	14.7	16.5	14.1	16.1	15.3
Thrombocytopenia								
Incidence	7.9	10.4	5.1	5.1	4.0	4.8	1.6	4.3
Prevalence	8.0	15.3	13.2	12.6	11.0	10.7	7.1	10.0
Constipation								
Incidence	4.5	4.0	2.4	1.7	1.8	2.4	0.9	1.3
Prevalence	4.9	7.3	6.6	6.8	6.3	6.9	5.9	5.6
Vomiting NOS								
Incidence	4.3	5.9	3.7	4.5	2.3	1.6	1.6	1.0
Prevalence	4.5	7.3	4.8	5.1	4.0	3.2	3.7	2.7
Anorexia								
Incidence	3.5	3.9	3.5	2.8	2 8	0.5	1.9	0.7
Prevalence	3.7	7.1	7.9	8.3	8.3	6.7	7.8	6.3
Pyrexia								
Incidence	5.7	3.9	1.7	3.2	1.3	1.6	0.6	1.7
Prevalence	5.7	5.4	2.8	4.7	3.8	2.1	1.9	2.3
Anemia NOS								
Incidence	4.3	5.1	1.5	3.4	0.5	1.1	0.9	0
Prevalence	4.4	7.4	5.5	7.3	4.5	5.1	5.9	5.3
Arthralgia								
Incidence	2.9	3.6	0.7	2.4	2.3	1.9	0.3	0.7
Prevalence	3.1	5.9	4.8	6.6	7.5	7.2	6.2	6.0
Headache NOS								
Incidence	5.9	2.5	0.4	1.1	1.3	0.3	0.3	0.3
Prevalence	5.9	4.5	3.1	3.2	3.3	2.4	2.5	2.0
Insomnia								
Incidence	0.9	1.4	0.9	1.5	2.3	1.3	0.6	1.3
Prevalence	1.5	2.5	3.9	5.1	6.8	8.0	8.1	8.0
Peripheral neuropathy NOS								
Incidence	0.5	2.9	2.6	2.8	5.3	3.5	2.5	2.3
Prevalence	0.7	3.4	6.8	8.3	13.0	11.7	13.0	13.6

Source: sponsor's table 12-4 clinical summary for protocol M34100-025

Reviewer's note: The index used in this table is number of events per 100 patient doses per cycle. Since there are 4 doses per cycle, the number of events may be considered to reflect the frequency per 25 patients per cycle. The prevalence of peripheral neuropathy increased with

additional exposure in cycles from 1 to 8 ($p<.01$, anova). Fourteen percent of patients experienced at least one grade 4 adverse event on study.

Table 46: Treatment-Emergent Adverse Events of Grade 4 Intensity, by MedDRA Body System and Preferred Term

	All PS-341-Treated Patients (n=202)
MedDRA Body System Preferred Term	**n (%)**
At least 1 adverse event	28 (14)
Gastrointestinal disorders	**5 (2)**
Diarrhea NOS	2 (<1)
Abdominal distension	1 (<1)
Diverticulitis NOS	1 (<1)
Vomiting NOS	1 (<1)
General disorders and admin site conditions	**3 (1)**
Weakness	1 (<1)
Nervous system disorders	**1 (<1)**
Neurological disorder NOS	1 (<1)
Blood and lymphatic system disorders	**11 (5)**
Thrombocytopenia	6 (3)
Neutropenia	6 (3)
Metabolism and nutrition disorders	**1 (<1)**
Hyperuricemia	1 (<1)
Infections and infestations	**2 (<1)**
Sepsis NOS	2 (<1)
Pneumonia, gram-negative	1 (<1)
Respiratory, thoracic, and mediastinal disorders	**3 (1)**
Respiratory failure	2 (<1)
Dyspnea NOS	1 (<1)
Pleural effusion	1 (<1)
Skin and subcutaneous tissue disorders	**1 (<1)**
Contusion	1 (<1)
Investigations	**1 (<1)**
Blood creatinine increased	1 (<1)
Renal and urinary disorders	**1 (<1)**
Renal failure NOS	1 (<1)
Cardiac disorders	**5 (2)**
Cardiac failure, congestive	2 (<1)
Pulmonary edema NOS	1 (<1)
Cardiac amyloidosis	1 (<1)
Cardiac arrest	1 (<1)
Cardio-respiratory arrest	1 (<1)

Source: Sponsor's table 12-5 clinical summary for protocol M34100-025

Table 47: Reviewer's Summary of Administered Dose and Toxicity in the phase 2 Studies.

protocol	study -024		study -025		
pro-forma dose level	**1.0 mg/m²**	**1.3 mg/m²**	**1.3 mg/m²**		
	n =28 patients	n =26 patients	n =202 patients		
			Cycle		
DOSE INTENSITY			**1**	**2**	**3**
Dose received % (a)	97% (10)	85% (20)	89 (17)	85 (20)	81 (21)
Doses missed % (b)	5	24	20	27	24
Doses reduced % (c)	0	13	3	9	16
ADVERSE EVENTS			composite total for -025:		
nausea	46%	62%	64%		
fatigue	68	73	49		
diarrhea	25	65	49		
periph. neuropathy [pn]	21	62	34		
pn ≥ Gr 3 (d)	7	15	12		
vomiting	14	38	36		
anxiety	14	35	11		
thrombocytopenia	32	27	44		
thrombocytopenia ≥Gr 3	29	15	28		
SAEs (all)	39	42	50		

a Ratio of actual dose to protocol-specified dose (+/-SD)

b. Percent of pts missing at least one of four doses per cycle through the third cycle

c. Percent of patients dose-reduced per cycle through the third cycle

d. PS-341 permanently stopped for 1 patient in the 1.0 mg group and 4 patients in the 1.3 mg group for pn.

3.1.3 SAFETY SUMMARY

The toxicity profile for VELCADE observed in the two phase II studies appears consistent with other cytotoxic drugs in early development. Typically, this clinical experience is limited by small sample sizes, quite ill patients with far-advanced malignancies with numerous baseline morbidities reflecting both the disease process(es) and prior therapies. Adverse events often cannot reliably be ascribed to a drug or the underlying disease process. Interaction of the new drug with other drugs or co-existing additional disease processes is speculative and uncertain. Estimation of the clinical benefit to safety ratio can at best be described as preliminary. Validation of surrogate markers/end-points will require experience in a much larger sample of patients over a much longer time interval. The current "best" evidence compiled from the effect of VELCADE on proteasome inhibition was measured by an assay on whole blood drawn one hour after bolus IV administration. Inhibition values ranged from 56-59% on day 1 to 69-73% on day 11. Over a 24 hour period, the mean % proteasome inhibition was constant at about 50% across a Cmax range of 10-90 (ng/ml). No apparent relationship was seen between the degree of inhibition of 26S proteasome activity at 1 hour after the first PS-341 dose on Day 1, Cycle 1, and

the incidence or severity of any category of adverse events including grade 3 and 4 adverse events, serious adverse events, and adverse events leading to study drug discontinuation.
A full characterization of VELCADE pharmacokinetics in patients receiving single agent VELCADE at the 1.3 mg/m^2 twice weekly monotherapy dosage schedule has not been reported. Therefore, the data are too preliminary to relate PK findings to safety, efficacy, special populations or drug interactions The safety population primarily reflects two small phase II studies in patients with advanced, progressive MM who had exhausted established therapy, including stem cell transplant in almost 40%. No comparator treatment arms are included. Traditionally, phase II studies have sought to estimate biological activity and to begin the accumulation of a safety database. Different populations of patients treated at different stages of their illness under different study conditions can be anticipated to result in different estimates of benefit and toxicity from those observed here. Further experience will be needed to define more clearly the role for VELCADE in optimal patient care.

3.2. Deaths

Study 024

One patient died on study, i.e., within 20 days of the last dose of PS-341; the primary cause of death, reported as pneumonia, was considered unrelated to study treatment by the investigator. Additionally, 7 patient deaths were reported more than 20 days after the last dose of study drug. Six of these 7 patients were reported to have died of progression of myeloma and for 1 patient multisystem organ failure was reported as the cause of death.

Study 025

A total of 11 patients (5%) died within 20 days after the last study drug dose or died of a cause considered to be study drug-related at any time after the last study drug dose. The cause of death was assessed as study drug-related for 2 (<1%) patients, and included cardiopulmonary arrest and respiratory arrest. In the other nine, progressive disease was at least contributory. Additionally, 55 patients died in the post-study period; for all 55 patients, the cause of death was considered to be unrelated to study drug.

4 Adequacy of safety testing

The safety population represents a population of advanced stage, previously heavily treated patients with MM, slightly younger on average than that of patients in community practice, who received VELCADE in a limited range of dose and schedule exposure. Adverse events were commonly encountered suggesting that near maximal dosing was achieved. The sample is likely to represent the usual patient with co-morbid illnesses and previous therapy. As such, for the specific labeled indication, the safety testing appears appropriate and credible.

5 Summary of Critical Safety findings and Limitations of Data

Study –024 and study –025 consist of a total of 256 patients, all with MM and all previously treated with numerous therapies including high dose chemotherapy and stem cell transplants in about one-third. Pre-existing hematologic and other organ toxicities were common, especially signs and symptoms of peripheral neuropathy. In a small group of patients (28) who received 1.0 mg/m2 twice weekly times two weeks each 21 days (dose intensity of 4.0 mg/m2 each 21 days, only 5% of doses were missed and 97% of the planned intensity was achieved. For the 1.3 mg/m2 groups, the average administered dose intensity was 1.1 mg/m2 per dose (or 4.4 mg/m2 each 21 days). Dose-toxicity responses were recognized for diarrhea and vomiting but not thrombocytopenia or SAEs. Increasing the number of treatment cycles produced an increasing prevalence of neuropathy. Duration and reversibility of neuropathy are uncertain at present. Dose limiting toxicities included peripheral neuropathy, diarrhea, thrombocytopenia, syncope/hypotension, fatigue and dehydration. Two-thirds of patients experienced at least one grade 3 adverse event. The toxicities were consistent across the phase I and II studies at once or twice weekly dosing in the range of 1.0 to 1.3 mg/m2 per dose. Also, most toxicities predicted by the animal studies were confirmed in patients. Treatment-emergent toxicities (adverse events) could be better appreciated with a control group for comparison. Use of VELCADE in combination with other cytotoxics or radiation has not been examined except for preliminary data in combination with gemcitabine. Accumulation of VELCADE occurs when given along with gemcitabine but is not characterized as a single agent given twice weekly. Also, exposure in special populations and the resulting toxicities have not yet been characterized. As a new molecular entity, there are no other studies of similar class drugs for comparison and no pharmacogenetic analysis has been completed.

VIII Dosing, Regimen, and Administration Issues

The recommended dose of VELCADE is 1.3 mg/m^2/dose administered as a bolus intravenous injection twice weekly for two weeks (days 1, 4, 8, and 11) followed by a 10-day rest period (days 12-21). This 3-week period is considered a treatment cycle. The twice-weekly schedule of PS-341 was chosen on the basis of pharmacodynamic studies in the rat and cynomolgus monkey. In these studies, proteasome inhibition in peripheral blood had a half-life less than 24 hours, with proteasome activity returning to pretreatment baseline within 48-72 hours after a single dose of PS-341. Intermittent but high inhibition (>70%) of proteasome activity was better tolerated than sustained inhibition. Thus, a twice weekly clinical dosing regimen was chosen in order to allow return of proteasome activity towards baseline between dose administrations. The recommended dose for phase 2 trials from a published phase 1 study was 1.56 mg/m^2/dose.[25] A re-evaluation of these same phase 1 trial results led to a decrease in the recommended phase 2 dose to 1.3 mg/m^2 based on the occurrence of 4 dose-limiting toxicities (DLT's) experienced in the cohort that received 1.56 mg/m^2. DLT's included Grade 3 diarrhea (3 patients) and Grade 3 peripheral sensory neuropathy (1 patient).

In study 024, a phase 2 dose ranging study of patients with multiple myeloma, there appeared to be marginally improved efficacy at 1.3 mg/m^2 compared with 1.0 mg/m^2. The primary conclusions regarding treatment efficacy were based on the overall response rate (ORR=

CR + PR + MR). The ORR to treatment with PS-341 alone was higher at 50% (13 of 26 patients) in 1.3 mg/m^2 dose group compared to 33% (9 of 27 patients) in the 1.0 mg/m^2 dose group. The rate of CR+PR to PS-341 alone was also marginally higher in the 1.3 mg/m^2 group: 38% (10 of the 26 patients) compared with 30% (8 of the 27 patients) in the 1.0 mg/m^2 dose group. The numbers were too small to reach statistical significance and so no definitive conclusions could be derived regarding the comparative efficacy of the two doses.

The 1.0 mg/m^2 dose appeared to be somewhat more tolerable than the 1.3 mg/m^2 dose. In the clinical trials under review, thirty nine percent of all patients on the 1.3mg/m2 dose completed the study, while 67% of patients on the 1.0 mg/m2 dose were able to complete the study (p=.0057). Twenty three percent of 230 patients receiving the 1.3 mg/m2 dose discontinued the drug because of an adverse event compared with 11% of patients on the 1.0 mg/m2 dose (p=.2). An approximately equal number of patients discontinued the study for lack of efficacy on either dose. Forty percent of doses were held or decreased in study 025 and over half of doses were held or decreased at the 1.3 mg/m2 dose group in study 024. The higher dose appears to be less well tolerated than the lower dose. Although there is insufficient data on efficacy at the lower (1.0 mg/m^2) dose to recommend the inclusion of this dose in the label, information should be provided concerning the tolerability and efficacy of the two doses so that providers can make a judgement regarding dose selection. Additional dose-finding studies are recommended.

The following dose modifications are recommended: therapy should be withheld at the onset of any Grade 3 non-hematological or Grade 4 hematological toxicities excluding neuropathy as discussed below. Once the symptoms of the toxicity have resolved, therapy may be reinitiated at a 25% reduced dose (1.3 mg/m^2/dose reduced to 1.0 mg/m^2/dose; 1.0 mg/m^2/dose reduced to 0.7 mg/m^2/dose). The following table contains the recommended dose modification for the management of patients who experience treatment-related neuropathic pain and/or peripheral sensory neuropathy. Patients with pre-existing severe neuropathy should be treated only after careful risk/ benefit assessment.

Table 48: Recommended Dose Modification for Treatment -Related Neuropathic Pain and/or Peripheral Sensory Neuropathy

Severity of Peripheral Neuropathy Signs and Symptoms	Modification of Dose and Regimen
Grade 1 (paresthesias and/or loss of reflexes) without pain or loss of function	No action
Grade 1 with pain or Grade 2 (interfering with function but not with activities of daily living)	Reduce to 1.0 mg /m^2
Grade 2 with pain or Grade 3 (interfering with activities of daily living)	Withhold therapy until toxicity resolves. When toxicity resolves reinitiate with a reduced dose at 0.7 mg/m^2 and change treatment schedule to once per week.
Grade 4 (Permanent sensory loss that interferes with function)	Discontinue treatment

NCI Common Toxicity Criteria website – http://ctep.info.nih.gov/reporting/ctc.html

IX Use in Special Populations

1 Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

1.1. Evaluation of Gender Effects on Efficacy

Of the 256 patients entered in both phase 2 studies, 44% (112) were female. No statistically significant difference between males and females in efficacy (response rate- 26% males, 29%-females) were found in the 2 phase 2 studies.

1.2. Evaluation of Gender Effects on Safety

No statistically significant differences between males and females in toxicity were found in the 2 phase 2 studies. Males patients had more grade 3 or 4 adverse events compared with female patients (85% and 76%, respectively). However, review of the data revealed no differences in incidence rates of serious adverse events or discontinuations due to adverse events between males and females. However, females were more likely to report musculoskeletal (72% females, 58% males), eye disorders (38% females, 24% males), and fatigue (60% females, 49% males). Males were more likely to experience thrombocytopenia (47% males, 34%, females), and respiratory disorders (61% males, 51% females).

2 Evaluation of Evidence for Effects on Safety or Efficacy in Subgroups

2.1. Evaluation of Age Effects on Efficacy and Safety

Among 202 patients in the single arm phase II study (025), 35% were age 65 or older. A marginally higher response rate was observed in patients <65 years of age (32%) as compared to patients ≥65 years (19%), but this response did not reach statistical significance (p=.064). The incidence of grade 3 or 4 AEs increased with patient age from 74% (patients ≤ 50 years) to 80% (51-65 years) to 85% (> 65 years). However, there was no apparent difference in the reported incidence of serious events and study discontinuation due to adverse events for those patients between 51 and 65 years and those > 65 years. The incidence of metabolism and nutrition disorders (e.g., anorexia, dehydration), vascular disorders (hypotension), cardiac disorders (tachycardia, congestive cardiac failure), respiratory disorders (dyspnea) increased with increasing age. Review of the most commonly reported adverse events revealed that anorexia and dehydration, as well as dyspnea NOS had incidence rates that increased with age categories and differed by more than 10%. The reported incidence rate of dyspnea NOS was higher in the 2 older patient groups relative to the younger patients with incidence rates of 8%, 23%, and 28% in patients = 50, 51 to 65 and > 65 years of age, respectively. Older patients were more likely to report constipation (45% 43%) during the study than those patients = 50 years of age (26%). Overall, the incidence of diarrhea did not reveal any apparent age relationship. However, the incidence of Grade 3 or 4 diarrhea increased by increasing age group, with 3%, 5%, and 13% of

patients = 50, 51 to 65 and > 65 years of age, respectively, experiencing at least 1 episode of Grade 3 or 4 diarrhea.

2.2. Evaluation of Race Effects on Efficacy and Safety

Over 80% of the phase II study (025) patients were white. Twenty-seven black patients and 20 asian/other patients were included in study 025. A marginally higher response rate was observed in Black patients (48%) as compared to White patients (24%) or patients of other races (33%); these differences did not reach statistical significance (p=.064). The number of Black patients and patients of other races was small relative to the number of Caucasian patients.

Overall no differences in incidence rates of Grade 3 or 4 adverse events, serious adverse events or discontinuations due to adverse events among subgroups based on patient race. Two adverse event categories reported differences between racial groups: musculoskeletal and connective tissue disorders, reported in 61% (white) compared to 81% (non-white) of patients, respectively, and psychiatric disorders (50% -white and 32%- non-white, respectively). Review of the most commonly reported adverse events revealed that white patients were more likely to experience fatigue (56%) than non-white patients (45%); diarrhea (50%, 38%) and pyrexia (38%, 25%) were also more frequently reported in white patients compared to non-white patients.

3 Evaluation of Pediatric Program

Multiple myeloma is not a disease of the pediatric population. However, the Children's Oncology Group (COG) is conducting a phase I study to determine MTD and phase II dose in children. To date, the study has enrolled 6 patients to date at a dose level of 1.2 mg/m2 twice-weekly for two weeks each 21 days.

4 Comments on Data Available or Needed in Other Populations

Although patients with renal impairment were enrolled in the phase 2 MM studies, no formal pharmacokinetic and pharmacodynamic assessments were made. In view of the problem of renal insufficiency in MM patients, a renal Impairment study should be conducted and include patients with severe renal impairment and those on hemodialysis.

Because VELCADE is metabolized by the liver, a hepatic impairment study should be conducted.

Although patients taking other medications were enrolled in the phase 2 MM studies No formal drug-drug interaction studies have not been performed and need to be conducted.

X Conclusions and Recommendations

Safety Conclusions

The safety database is comprised of 379 patients with advanced, previously treated malignancies from five studies where VELCADE was used alone and one study in combination with gemcitabine. In the four phase I studies, dose escalations were conducted with once or twice weekly IV dosing schedules for two to four weeks. The two phase II studies, with a total of 256 patients with MM, used the twice weekly times two weeks schedule and represent the efficacy database for accelerated approval. Clinical experience generally followed pre-clinical observations except that the acute cardiovascular mortality in monkeys at doses of ≥3.0 mg/m2 or more has not been described in humans. Single doses of up to 2.0 mg/m^2 once per week have been administered to adults. VELCADE monotherapy PK has not been completed. Available pharmacodynamic data does is too preliminary to indicate a dose-response or dose-toxicity relation. The database is too preliminary to describe the safety of VELCADE in special populations (hepatic or renal impairment patients) or in combination with other drugs or in pediatric patients.

Expectant monitoring of hemodynamic, gastrointestinal (GI) and neurologic toxicity should be emphasized. The frequency and severity of diarrhea are dose dependent. At single weekly doses above 1.5 mg/m2, orthostatic hypotension and diarrhea were dose-limiting. Since myelosuppression is not a dominant toxicity, other organ toxicities may become dose-limiting in the absence of hematologically based dose reductions. Reference to the NCI CTC website should be added to the label (http://ctep.info.nih.gov/reporting/ctc.html) to assist oncologists in the recognition and monitoring of the less common organ toxicities. The proposed vial size may pose a hazard to human use as described above. Further studies are planned to evaluate the above concerns.

Efficacy conclusions

In the studies under review, PS-341 demonstrated efficacy and safety in the treatment of multiple myeloma (MM) after at least 2 prior therapies. The primary efficacy endpoint was response rate, according to a variety of response criteria (see introduction). The FDA was able to confirm 5 CR^{Bladc} responses in the relapsed and refractory population for a CR^{Bladc} response rate of 2.6% (95% CI 1,6). Some evidence of clinical benefit including increased hemoglobin and platelet counts, decreased transfusion requirements, and increasing physiologic immunoglobulins accompanied these responses. Two patients with CR^{Bladc} responses had been heavily pretreated with multiple prior regimens including stem cell transplant. One of these patients had a deletion of chromosome 13, considered a poor prognostic sign. The FDA analysis of response duration, which included data from the extension studies, confirmed an overall Kaplan-Meier estimate of median of duration of CR+PR of 365 days.

In study 025, PS-341 was administered at a 1.3 mg/m2/dose intravenously twice weekly for two out of three weeks for up to 8 cycles to 202 patients with MM who had received at least two prior therapies and demonstrated disease progression on last therapy. Fourteen patients were excluded from the analysis. In the 188 patients in the final analysis population, a complete response rate of 2.6% (n=5) and a partial response rate of 27% (n= 53) was demonstrated. Supportive evidence of efficacy was provided by a small phase 2 dose-ranging study in MM, in which 53 patients who had received at least two prior therapies received either a 1.0 mg/m2/dose or a 1.3 mg/m2/dose twice weekly for two out of three weeks. A single complete response was

seen in each dose cohort, and an overall 30% (8/27) CR+PR rate at 1.0 mg/m2 and a 38% (10/26) CR+PR rate at 1.3 mg/m2 was noted.

Study 025 population enrolled a somewhat heterogenous group which included 3 patients who had received only corticosteroids and biaxin as well as 63 patients who had received multiple stem cell transplants and other therapies. Study 024 was in general less heavily pretreated and included 5 patients who had received only corticosteroids. The relatively lightly pretreated patients were excluded from the FDA efficacy analysis for the refractory indication. If the relatively lightly treated patients are excluded, then the study populations from study 025 and 024 could support the proposed indication of relapsed and refractory myeloma.

Additional response analyses were performed to confirm the clinical benefit of PS-341. 12 patients achieved a 100% reduction of the serum or urine M-protein for a median of 96 days. Five (41%) of these patients relapsed and the median duration of this category of response was 96 days. A total of 30% of all patients achieved a CR or PR (50% improvement in M-protein). This partial response rate is similar to those reported in studies using thalidomide and dexamethasone and the experimental therapy CC5013 but lower than that reported in studies of relapsed and refractory patients undergoing autologous transplant. Partial responses were seen across a variety of subgroups including patients who had undergone transplant and high dose therapy, patients with elevated B-2 microglobulin, chromosome 13 deletions and elderly patients. Patients with CR^{Blade} appeared to have durable complete responses. Patients with more complete clearance of their myeloma protein appeared to have longer duration of survival than those with less complete clearance of their myeloma protein, although this analysis is methodologically flawed. CR^{Blade} responses may predict for improved survival and increased time to progression, and they are quite unusual in patients with relapsed and refractory myeloma not treated with high dose chemotherapy followed by stem cell transplant.

Recommendations

Safety evaluation is adequate for marketing under accelerated approval for this indication. Areas of limited safety experience have been noted above. These concerns will be expressed in the labeling and included in phase 4 commitments. Special attention should be given to (1) the uncertainty of the degree and reversibility of cumulative neuropathy with more prolonged drug exposure and (2) adverse cardiovascular reactions including hypotension and syncope which may be drug-related and/or influenced by the patients' underlying hydration and cardiovascular reserve. In addition, sponsor should assist clinicians with additional education in the recognition of and dose-adjustment for non-hematologic toxicities of anti-neoplastic drugs, including reference to the CTC webpage in promotional materials.

Durable complete responses may be considered to be evidence of clinical benefit.[1] Blade criteria for complete response have not yet been validated as evidence of clinical benefit for registration in MM, particularly outside the context of transplantation, but there is sufficient support in the literature to suggest that these criteria are a surrogate, 'reasonably likely to predict' clinical benefit. Based on a literature review and the advice of practitioner consultants, the partial response rate was also considered to be a surrogate for clinical benefit. Based on a review of the literature and the advice of practitioner consultants, the partial response rate was also considered to be a surrogate for clinical benefit, however, insufficient patients with CR (Blade)

responses were reported to consider VELCADE for full approval. Additional clinical benefit analysis of the patients exhibiting partial responses, including improved survival in these patients, provided further support for the concept that these patients received clinical benefit. We therefore recommend Accelerated Approval, under CFR§314.510 Subpart H, for the treatment of MM in patients who have received at least two prior therapies and have demonstrated disease progression on last therapy. Confirmation of clinical benefit may be based on an analysis of the ongoing phase 3 study 039 in MM.

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